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PROCEEDINGS OF A SEMINAR ON FUTURE RESEARCH NEEDS IN LYMPHATIC FILARIASIS

8-10 OCTOBER 1990

Vector Control Research Centre
Pondicherry-605 006
India.

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COMMUNITY HEALTH CELL
326, V Main, I Block
Koramangala
Bangalore-560034
India

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FOREWORD

Lymphatic filariasis is one of the most important vector borne disease problems of India: over one third of all the people at risk of filariasis live in this country. This disease has never received adequate attention from health planners and has, until recently, been largely neglected by researchers. Efforts to control the disease have been very relatively unsuccessful, and the problem continues to increase both in magnitude and direction.

From its inception in 1975 the Vector Control Research Centre identified Filariasis as a major area of research. Extensive studies were undertaken initially on all aspects of the ecology of the vector *Cx. quinquefasciatus,* studies which formed a landmark in understanding the dynamics of the vector population. Encouraged by this success, the VCRC undertook a five year Integrated Vector Control project at Pondicherry from 1980. Even though the vector population was successfully controlled by this programme, an impact on human disease proved difficult to demonstrate with the epidemiological tools then available. Despite the voluminous entomological and parasitological data available for analysis, the evaluation was hampered due to a lack of proper understanding of the disease processes and the dynamics of transmission.

Parasite epidemiological studies were therefore initiated in collaboration with the Imperial College, London. Several publications have been brought about both in national and international journals. These have provided an insight into the complex dynamics of infection and disease. However, it has also indicated the existence of several lacunae in our understanding of the disease process. During the past 15 years, the VCRC has developed expertise in several areas of filariasis research which include entomology, parasitology, clinical aspects, chemotherapy and socio-economic aspects. The work carried out by the VCRC has earned increasing recognition from the international community of scientists. The important fields that need strengthening are immunology and basic biology of parasites. At this juncture, it is necessary to review the present knowledge so that the future areas of research can be identified.

Several research groups in many parts of the world have been working in isolation on different aspects of the disease. This approach has achieved some important recent advances: management of lymphoedema has been advanced by the development of lympho-nodo-venous surgery; Ivermectin has raised new hopes for disease control; identification of stage specific antigens has increased the possibility of developing immuno-diagnosis tools; new light has been thrown on the immuno-pathology of disease without microfilaraemia. The unique,

voluminous database at the VCRC has contributed to this by opening up new avenues in understanding the dynamics of disease, and it is hoped that a generalized mathematical model will emerge soon. Nevertheless, our knowledge gaps remain unacceptably wide in several areas. There are no good studies on the natural history of the disease. No one knows what are the risk factors, and whether the progression of disease is a sequential phenomenon. We have no idea of what actually precipitates the episodic filarial fever attacks. It is unclear whether these are one or more strains of parasites. Several immunodiagnostic tests have been developed in different laboratories in India, but none has been found to be reliable in detecting asymptomatic parasite carriers (microfilaraemic or amicrofilaraemic). The social and economic impact of this disease has not been quantified. The epidemiology of the disease in rural and urban areas has not been studied in detail. Present strategies developed for urban areas require major modifications. It is still unknown whether chemotherapy, vector control, or an integrated approach offers the best hope for control success.

A considerable body of research has been undertaken in India but too much of this has been of the "Me-too" type, wherein scientists have faithfully reproduced or confirmed work done at other laboratories rather than develop new initiatives. The present seminar brings researchers from all over the world and from different specialities with the aims of reviewing the current state of knowledge and of highlighting the research priorities, with particular reference to the situation prevailing in India. It is intended that this will prevent duplication of efforts and promote interdisciplinary co-operative efforts. Finally, it is hoped that the seminar will not only encourage scientists to interact, but will also stimulate our new generation of young scientists by opening up new channels of thinking.

Dr.P.K. Rajagopalan
Director
Vector Control Research Centre

8th October, 1990.

INAUGURAL ADDRESS

BY

Dr. S.P. Tripathy
Addl. Director General
Indian Council of Medical Research

Dr. Tripathy conveyed the good wishes of the Director General, Prof. A.S. Paintal, and his full support and encouragement for the success of the Seminar. The Council hopes that the Seminar will provide a direction for research into the Control and Management of Lymphatic Filariasis which will act as a blueprint for research over the next decade and beyond.

The representative of the W.H.O., Dr. C.P. Ramachandran, the visiting experts from abroad, the members of the Scientific Advisory Committee, and all the scientific participants at the Seminar were extended a warm welcome. It was particularly hoped that the Director of the National Filariasis Control Programme, Dr. M.V.V.L. Narasimham, the "end user" of filariasis research, would actively participate in the Seminar and benefit from the proceedings.

The VCRC had never looked back, but only moved forward during its 15 years of existence. This outstanding success was attributable to the dynamic leadership of the 'evergreen' Director, Dr. P.K. Rajagopalan, who has all the qualities of an ideal scientific director. Dr. Tripathy emphasised that a large share of the credit for this must also go to the unstinting support of Mrs. Rajagopalan.

The VCRC has developed excellent teams of workers, not only in the Pondicherry Centre, but also in the Field Stations. The programmes at Shertallai and Koraput are brilliant examples of what can be achieved in field research, and their success has encouraged the Council to support such activities in other areas.

The Council has actively promoted intersectoral collaboration in control as a means of achieving sustainability. In practice, however, true collaboration has rarely been achieved. The work in Shertallai is a notable exception to this, and is a shining example of a genuinely collaborative control programme.

The last 15 years have seen the VCRC grow from infancy to maturity. The Centre has

developed a multidisciplinary approach, using specific technology which is appropriate to particular control needs. The range of approaches includes biological control, civil engineering techniques, mass chemotherapy, IVM and combinations of all of these. In adopting this enlightened approach the VCRC has provided an example which it is hoped that other ICMR institutions will follow.

The VCRC started as a Centre for research on vector control, but has grown into a much larger institute with research encompassing not only vector control but also disease control. The VCRC has taken over the role of a National Institute of Filariasis Research - and can rightly be called this. Dr. Tripathy stressed that such a change of name would be acceptable to the Council and the Government without any hesitation.

It was hoped that the NFCP would perceive the VCRC as a national level institute, belonging not just to ICMR but to the Government and the Nation, and would use the VCRC to assist the development of the NFCP.

The VCRC has played a major role in manpowers development. Appropriately trained medical entomologists were almost unavailable in India - no University offered training in this discipline - until the M.Sc. Medical Entomology course was established at VCRC. The Centre has also supplied numerous Ph.D level scientists who have provided excellence in research at VCRC and elsewhere.

Dr. Tripathy expressed his gratitude to W.H.O for support, first through a Research Strengthening Grant and then through assistance to the M.Sc. course. He noted that the representative of W.H.O had stated that the VCRC was a unique institute with which he hoped to maintain a long association. Dr. Tripathy hoped that Dr. C.P. Ramachandran would carry this message to the Steering Committees of W.H.O in order that support from W.H.O might continue. W.H.O support is critical to achieving flexibility to respond to research and training needs, particularly in the current economic climate.

With the retirement of Dr. Rajagopalan, the VCRC would now enter a new phase of its development. It was hoped that the new Director will rise to the challenge of achieving continuing growth, and the ICMR would provide its support for this. Hopefully, the W.H.O would do the same.

Dr. Tripathy emphasised his support for the further development of the recently created

Epidemiology Division, and in particular the existing development of experimental models. It was also hoped that the Centre would make use of the spectacular advances in biotechnology and immunology, and incorporate these in future research activities.

In concluding, Dr. Tripathy thanked Dr. P.K. Rajagopalan and Mrs. Rajagopalan for the help they have given, and the sacrifices they have made, to make the VCRC the outstanding success it is today.

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1. RESEARCH PERSPECTIVES

P.K. Rajagopalan & D.A.P. Bundy

Human infection with *Wuchereria bancrofti* or *Brugia malayi* is collectively known as lymphatic filariasis. It is estimated that several hundred million people are at risk of infection, and that approximately 90 million are currently infected. Endemic areas are found throughout the tropical zone, but nearly half of all people at risk are in India. Surveys conducted over the last 30 years indicate that both the distribution and prevalence of infection in India is increasing. This is partly the result of more intensive survey effort, but probably also reflects a real increase : the large scale development of urban areas has provided extensive new habitats for the vector mosquito, *Culex quinquefasciatus*, and hence new or more extensive endemic foci for bancroftian filariasis.

The control approaches that are currently adopted in India and elsewhere involve vector reduction (through environmental modification, larviciding or IVM) combined with chemotherapy programmes. Vector reduction has proven in practice to be a difficult, long term and often costly process. Chemotherapy also requires long term and regular commitment, because the most widely used anthelmintic (DEC) is effective against the larval rather than the adult stage and because the irreversible chronic disease effects can only be avoided by early and repeated treatment. Given these constraints it is unsurprising that current attempts at control have met with limited success.

When considering future goals in filariasis research two aims are pre-eminent: the development of improved control tools; and the enhanced efficiency of application of existing (and future) control tools. The first aim is being pursued through the assessment of new chemical and biological agents and is the subject of considerable effort internationally and at VCRC. How best to pursue the second aim is the subject of this meeting.

Because of the complexity and cost of current control strategies it is clear that affordable, sustainable and effective control can only be achieved by maximising the efficiency of control design. Large-scale and long-term control of disease will inevitably be difficult to operationalize and it is essential that the most efficient design is selected for implementation. What are therefore required are rigorous and quantitative methods of selecting the optimal control strategies.

Identifying the most cost-effective method of reducing the disease caused by filarial infection is the major goal of VCRC, and it is towards this goal that future research must be orientated.

The biology of filarial infection and disease is complex (Fig.1), yet an understanding of these processes is essential to an understanding of control. In order to identify the knowledge gaps that need to be filled by future research it is necessary to consider: the dynamics of infection; the relationship between infection and disease; the effects of control interventions on the dynamics of infection; and the socio-economic implications of the various control tools. Only with this knowledge is it possible to assess the cost effectiveness of control interventions (Fig.2). The current status of knowledge in these areas is outlined below:

Socio-Economic Issues: This is an area of filariasis control which has been almost entirely overlooked. Yet the issue of cost is of major relevance to the sustainability of, necessarily long-term, control activity, as are health education and community empowerment. Accurate cost data, linked to precise epidemiological description of control outcomes, are currently available but could be readily assembled as a component of existing control activity.

Infection Dynamics: Current knowledge is extensive but by no means complete, and is largely based on classical parasitology and entomology. These disciplines have made a considerable contribution but , as the following review should make clear, some of the central issues can only be resolved by a fresh initiative involving the new disciplines of parasite epidemiology (population biology), immunology and molecular biology.

Infection Processes: It has been estimated that between 2,000 and 100,000 infective mosquito bites are required to achieve patent infection. These enormous numbers are difficult to reconcile with the continuing persistence and spread of infection. Whether these estimates truly reflect inefficient transmission, or are a consequence of host acquired immunity, is crucially important to the design of future control approaches; if the former, then vector control might be a preferred option, if the latter, then new approaches such as age targetting or vaccination would be more worthy of consideration. Quantifying the role of host resistance requires longitudinal studies in which both immunological and epidemiological variables are assessed.

Infection Patterns: The age-distribution of the prevalence of infection has been described in a number of studies. These data are now recognised to be under-

estimates - due to a combination of statistical sampling error and methodology - but are probably adequate for present purposes. Obtaining adequate data on the age-profile of infection intensity, however, continues to be a major problem. There is no method at present of directly estimating the number of adult worms in an infected individual, thus intensity is estimated indirectly from the number of larval stages in the peripheral circulation. The reliability of this procedure is unknown.

The Role of Vectors: Vectors are important to the infection process at the individual level, as discussed above, but they are also crucial to an understanding of patterns of infection in the community. Vector biology has been the subject of extensive investigation, but only rarely have vector studies been directly correlated with human host infection patterns. Areas of particular importance here include the role of spatial distribution of vectors, seasonal changes in vector infection patterns, and the effects of host age and gender on vector biting patterns.

Disease Patterns & Morbidity: The classical disease manifestations of filariasis at the individual level have been thoroughly described. What is less well known is the pattern of disease occurrence within communities, particularly the time scale of the progression through the various disease stages and the effect of chemotherapy on this process. The major question, however, is how disease relates to infection; available data indicate that there is a significant difference between the age-prevalences of disease and infection, and that this difference varies between endemic areas. Current explanations for this discrepancy range from individual differences in immune responsiveness to community differences in rates of exposure to infection. Resolving this issue is central to defining control approaches which will reduce morbidity; the major aim of any control programme.

Identifying which aspects are most immediately deserving of research is a difficult process requiring a rigorous and quantitative framework for selection. In approaching this task the VCRC has adopted a quantitative approach based on the flow diagrams in Figures 1 and 2. This is intended to ensure not only that the research is goal-oriented but also that the studies form part of a logical progression towards achieving the goal. Developing an Integrated Research Programme is the major aim of the meeting.

Two questions must be asked in identifying research needs: is the information necessary to understanding the process of Figure 2; and is the research feasible ? A clear distinction must be

made between what is "do-able" now, and what will produce results only in the long term. There must also be realism in assessing technological requirements: where should research be conducted ?

In briefly reviewing these areas one conclusion becomes immediately apparent: the major issues can only be addressed by multi-disciplinary research teams. Resolution of the central issues requires epidemiological, immunological and clinical research to be applied in parallel. Furthermore, the time-scale and the population patterns of infection and disease require the research to be conducted on a large scale over a long period. The development of a new initiative in filariasis control is a challenging task, but it is a task which the ICMR and the VCRC are uniquely well qualified to undertake.

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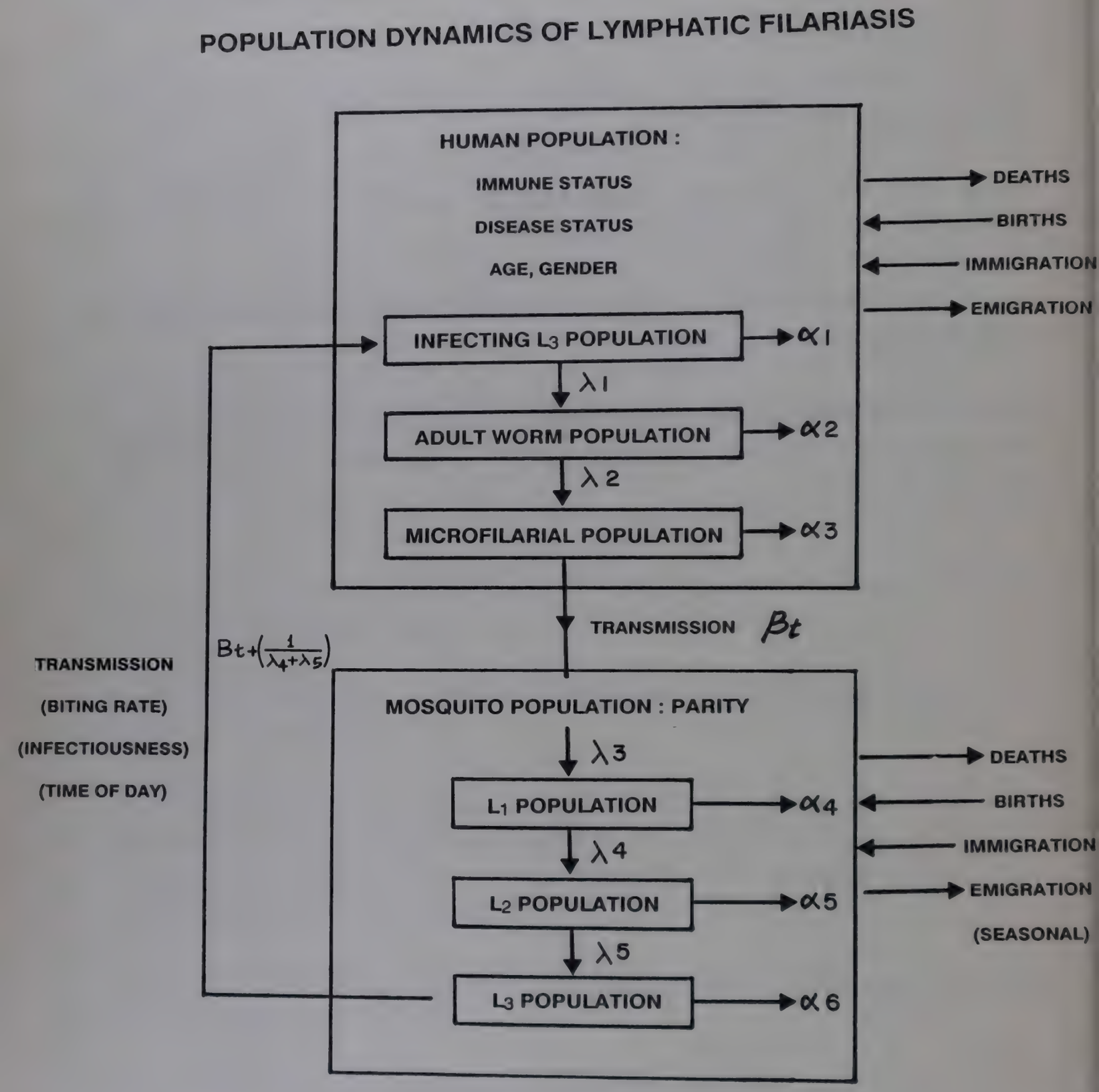
POPULATION DYNAMICS OF LYMPHATIC FILARIASIS
HUMAN POPULATION :
IMMUNE STATUS
DISEASE STATUS
AGE, GENDER
DEATHS
BIRTHS
IMMIGRATION
EMIGRATION
INFECTING L3 POPULATION
α1
λ1
ADULT WORM POPULATION
α2
λ2
MICROFILARIAL POPULATION
α3
TRANSMISSION
βt
Bt+(1/(λ4+λ5))
TRANSMISSION
(BITING RATE)
(INFECTIOUSNESS)
(TIME OF DAY)
MOSQUITO POPULATION : PARITY
λ3
L1 POPULATION
α4
λ4
L2 POPULATION
α5
λ5
L3 POPULATION
α6
DEATHS
BIRTHS
IMMIGRATION
EMIGRATION
(SEASONAL)

FIG. 1.

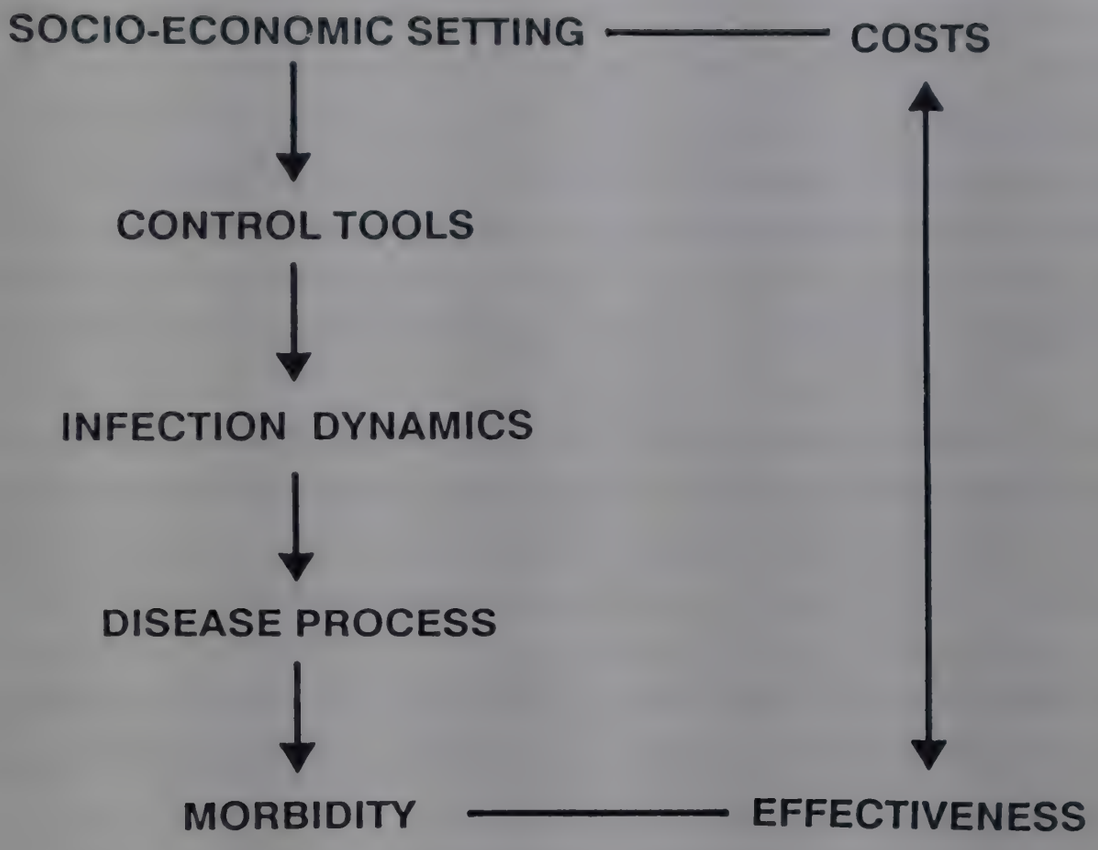
SOCIO-ECONOMIC SETTING
COSTS
CONTROL TOOLS
INFECTION DYNAMICS
DISEASE PROCESS
MORBIDITY
EFFECTIVENESS

Fig. 2

2. PERSPECTIVES ON PATTERNS OF INFECTION

P.K.Das

The population dynamics of filarial parasites is complex and the identification of factors responsible for generating such complexity is a central theme of the infection process. Epidemiologists rely heavily on microfilaria rate as a measurement of prevalence. This is not a very sensitive tool to measure true prevalence and also conceals the variability within the population. Since the identification of the factors generating this variability is a major concern of the epidemiologist, it is important to highlight such variability. Variability can arise either due to sampling procedures or due to the inherent variability of biological systems.

One of the most useful tools for the study of the inherent variation in the population is the frequency (Probability) distribution of infection. Such patterns are extensively used to describe the dynamics of intestinal nematode parasite populations of intestinal nematode where adult worm burden can be directly assessed (Anderson and May 1985; Bundy 1988).

The availability of the extensive data set, collected by the Vector Control Research Centre during 1981-89, has made it possible to use detailed frequency distributions as a tool to highlight certain aspects of the transmission dynamics of infection and disease.

Frequency distributions of mf counts in general show highly overdispersed distributions, and the negative binomial model gave a simple measure of overdispersion (Das *et al.,* 1990). The estimated zero probability of the fitted distribution, was used to calculate the proportion of each age group which has a true zero count (corrected for sampling errors) using the equation given by Grenfell *et al.* (1990), and hence it was possible to estimate the corrected prevalence of infection.

Since an overdispersed distribution can be generated either by differential exposure over a period of time and/or heterogeneity in the host's capacity to develop an immune response, changes in the pattern of infection over time were studied by examining age-specific prevalence. Both the observed age-specific prevalence and the prevalence corrected for the zeros arising out of sampling procedure showed a relatively rapid rise in prevalence in the younger age classes followed by a plateau and slight decline in the adults. Although the age-prevalence pattern was similar for both estimates, the corrected age prevalence curve indi-

cated a higher absolute level of prevalence.

Even the corrected age prevalence of mF conceals some sources of variability since it does not indicate the force of infection which is probably more crucial for defining the relationship between infection and disease. This can be estimated from mf density data which may provide indirect evidence of the adult worm burden.

Analysis of the age intensity curve showed that the intensity increases monotonically in the younger age classes, forming a plateau and then declining slightly and stabilizing in older age classes.

Such age-dependent patterns of infection can arise either due to differential exposure with age or increased resistance to infection with age or some combination of both processes (Vanamail *et al.,* 1989). It has been suggested that the man biting rate increases from childhood to adult due to the growing surface area of the body, and then stabilises in the adult age class after growth ceases.

Whether host resistance is responsible for such age-dependent variation was then tested by estimating the age-specific rate of acquisition and loss of infection. Using a catalytic model and longitudinal data sets, age-specific rates of loss and gain were calculated.

The analysis revealed that the gain rate increases with age up to 16-20 years and then declines. Since the biting rate (= exposure) appears to be constant in adults this implies that over the age of 20 immune mechanisms developed by individuals with a history of infection is effective against the aquisition of new infection. This effect was apparently unsuccessful in clearing old infection since the loss rate was independent of age. The immunity probably functions against the infective stage, and not against the adult or microfilaria.

The observed mean mf density for each age group reflects an underlying overdispersed distribution of counts.

The variation in the age dependent intensity was explored by estimating m mean and dispersion parameter k for each age class. This indicated that while there was no significant trend in m with age k increased linearly with age. This demonstrates an age-dependent decrease in overdispersion, which is consistent with the development of acquired immunity.

To compare the population dynamics of *W.bancrofti* and *B.malayi* the Shertallai field station data were subjected to similar analysis. The analysis showed that the observed age-specific prevalence and intensity were similar to the overall picture of bancroftian filariasis in Pondicherry. However, an age related decline in overdispersion was not demonstrated. This may imply that immunity is less important on the aquisition of infection and is not age dependent.(Srividya *et.al* 1990). It may also reflect the very low rates of infection in the Shertallai focus.

While this explains some aspects of the dynamics of the parasite population, it still conceals some individual variation, which might arise due to differential exposure (due to variation in attractiveness of individuals or living condition),genetic variability of the host or strain variations in the parasite.

In order to examine the consequences of the general observation that individuals who develop chronic disease are mf negative, mf male individuals were partitioned into those attributable to the sampling procedure and the excess negatives and the disease prevalence were superimposed on the excess. This showed a steady increase of disease with age.

Further studies to examine the relationship between the dynamics of *W. bancrofti* infection and the development of chronic lymphatic disease also indicated that in endemic populations those who develop disease progress through the sequence: uninfected, microfilariaemic, amicrofilaraemic to develop irreversible obstructive lymphatic pathology.

It is important to stress that this analysis was only possible because of the extensive clinical, parasitological and vector data sets collected over a period of 9 years by VCRC.

Spatial Heterogeneity:

Another important source of variability in infection pattern is spatial heterogeneity. One of the problems here is the lack of compatability between data sets. In examining 17 major filariasis data sets from different locations in India we realised that the methodology adopted in each study was different and that the data were comparable only for four studies. Comparision of results showed a wide variation in the pattern of infection and disease. However, it is difficult to define how much of this variation is due to population dynamics of the parasite and how much is due to different methodologies. Failure to recognise the importance of variation in data quantity can give misleading conclusions. For example, it has been suggested that

the incidence of hydrocele is different in southern and nothern India. However, analysis shows that when truly comparable studies are used then no such difference exists. Therefore there is a need to define clinical symptoms and all future epidemiological studies should follow a standard protocol.

While geographical variation on the large scale has received the attention of scientists, epidemiological heterogeneity at the microlevel has been largely neglected, yet this may be important. For example, when the Pondicherry data set was analysed at the macrolevel we found that the biting density and resting density of mosquitoes, and the frequency distribution of parasites in man and the vector were more or less homogeneous. However, when the sample data were analysed at the microlevel, considerable heterogeneity was observed. Microlevel heterogeneity is of growing interest in ecology in general and can influence the pattern of infection and disease. This is clearly an area deserving of further research.

In conclusion I would like to emphasize that the complexity of filarial disease calls for precise data sets which should not only estimate mf rate and intensity, but also should determine the immunological status of the subjects studied. In designing epidemiological studies greater prominence should be given to microlevel epidemiological variation in influencing the pattern of infection and disease. These epidemiological analyses indicate that the intensity of exposure over a period of time is a crucial determinant of patterns of infection. How continuous exposure or interrupted exposure changes the pattern of disease needs to be elucidated by comparing the epidemiology of filariasis in areas where seasonal transmission takes place with areas where perennial transmission occurs.

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3. PERSPECTIVES ON IMMUNOPATHOLOGY IN LYMPHATIC FILARIASIS

E.A. Ottesen

The most significant pathology associated with bancroftian and brugian filariasis is localized in three organ systems: the lymphatics (acute inflamation, oedema, hydrocele, elephantiasis and chyluria), the lung (tropical pulmonary eosinophilia syndrome) and the kidneys (haematuria, proteinuria). Clearly, some of this pathology is immunologically mediated; but equally clearly, some is not.

When the host interacts with the parasite, the response is primarily an "immune response", and this immune response varies between different individuals. It has been suggested that the amount of pathology induced by filarial parasites is proportional to the vigour of the host's immune response. The evidence for this is the comparatively high filarial antigen specific responses (e.g. lymphocyte proliferative response, cytokine production, antibody production etc.) in patients with elephantiasis when compared to those whose filarial infections were manifested as asymptomatic microfilaraemia.

Though the whole story is probably not so simple (as we shall see later), it is true that these pathology syndromes in filariasis are associated with vigorous immune responses, the most extreme example being the tropical pulmonary eosinophilia syndrome. This syndrome was first formally described in India, and the best work on its pathogenesis and treatment has come from here too. Basically, TPE is characterized immunologically as a syndrome of very high antibody responsiveness, especially IgE antibody. The quantitative levels of this IgE, for example, are 10-100 fold higher than the levels seen in patients with other manifestations of filariasis, and the range of different filarial antigens recognized by this IgE is also much broader. The pathogenesis of this clinical syndrome has been inferred as follows: the very high levels of antibodies include IgE opsonins that bind to microfilariae essentially as soon as they are released from an adult worm. These opsonins cause the microfilariae to be filtered out in the lung, where they initiate inflammatory reactions, are killed and release their antigens. These antigens trigger the I_gE-coated mast cells whose mediators (including histamine and eosinophil chemotactic factors) are released and cause greater inflammation, including a massive eosinophilic infiltration (as defined by pulmonary lavage). These eosinophils degranu-

late and release toxic granules that cause severe interstitial fibrosis unless treated appropriately. Even though TPE is the filarial immunopathology syndrome that is the most well understood, there remain significant challenges for **Future Studies,** that include definition of why an individual with filarial infection develops this unusual syndrome in the first place and how the destructive eosinophilic pneumonitis (which persists even after DEC treatment) should best be managed. Answers to these questions have implications not just for TPE but for all other pulmonary eosinophilia syndromes as well.

With respect to our major concern in filarial pathology, i.e. the lymphatics, it has been suggested already that affected patients with elephantiasis or hydrocele appear immunologically more responsive than those with asymptomatic microfilaraemia, but how such responses translate into lymphatic pathology is less certain. What has become clearer during the past decade is that there are two "forces" at work to cause this pathology - one immunologic and the other not. This conclusion first came from studies of *Brugia malayi* infection in nude mice. Such mice lack a functional immune system, yet develop huge, dilated lymphatics and elephantiasis after infection. If made immunocompetent by reconstitution experiments, they will form granulomatous reactions around the worms and subsequently will develop obstructtive lymphatic lesions. Clear histopathologic correlates to the findings in humans exist, and the concept that two types of lymphatic damaging processes - one immunological and the other not - but both causing lymphatic functional decompensation and elephantiasis, is now well established. **Future Studies** designed to understand the pathogenesis of these lymphatic lesions can take advantage of both the *in vitro* studies of vascular and lymphatic endothelial cell cultures that can be challenged with parasite products and immunologically induced cytokines, and the *in vivo* models of elephantiasis in a variety of animals whose immune systems can be manipulated and assessed. The findings should be important for all diseases involving the lymphatics.

While the concept that increased immune responsiveness to parasite antigens determines enhanced pathology has been a useful one, it is becoming increasingly clear that it is not completely correct. In both humans and experimentally infected animals, lymphocyte proliferation responses, for example, are known to be minimal or absent when blood lymphocytes or spleen cells are challenged by parasite antigens during chronic infection. What is becoming increasingly obvious, however, is that this decline in responsiveness to parasite antigen as the infection becomes chronic represents not a **loss** of immune responsiveness but a **gain** in immune responses that are inhibiting or regulatory in nature. Similar conclusions can be found in the data from studies of "blocking antibodies" that serve to control or modulate allergic respon-

siveness to parasite antigens. In distinct contrast to the finding with most other antibody levels that have been measured, TPE and elephantiasis patients have **low** levels of blocking antibody while asymptomatic microfilaraemics have **very high** levels. Evidence indicates that these blocking antibodies are of the I_gG4 subclass, a subclass not commonly stimulated by most antigen challenges. Since such antibodies could be very important in controlling IgE mediated inflamation, not only in filarial infections but in allergic diseases as well, **Future Studies** to determine ways in which I_gG4 responses can be selectively induced, and definition of the control mechanisms responsible for I_gG4 production (probably linked to IgE production) will be very valuable.

The main point of all these examples of the immune response to filarial infection is that such responses are very high in all patients with filariasis; it is just that the character of the responses is different. Some individuals have primarily effector responses and others primarily suppressive or regulatory responses. What causes individuals to differ in their responses to the "same" infection is entirely unclear. There may be genetic predispositions or restrictions inducing the different patterns of responsiveness, and while earlier studies generally failed to detect HLA associations, the probes for analysing HLA associations (and the "immune responses genes" they encompass) are so much better today (including Restriction Fragment Length Polymorphisms (RFLP) and PCR amplifications of HLA-D regions (DQ, DR, DS) with subsequent probing) that the potential genetic associations with clinical syndromes (especially TPE) should be re-approached in **Future Studies.**

Similarly, much of the susceptibility and clinical diversity among infected individuals may relate to pre-natal exposure to parasite antigen that results in modulation (tolerization) of the newborn's response to subsequent parasite infection or challange. Already there is good evidence in humans that there is pre-natal sensitization to filarial antigens in children born to infected mothers in Madras (based on cord blood IgE findings), and though there is no direct evidence in humans that clinical manifestations or pathology are altered in such individuals, animals model studies show that pre-natal sensitization does alter the subsequent pathology in infected offspring. Clearly, this subject is relevant to many diseases other than filariasis, and **Future Studies** of maternal and genetic influences on the subsequent development of immunopathology could have a major impact on our understanding of both filariasis and many other endemic infectious diseases.

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4. THE CLINICAL PERSPECTIVES AND RESEARCH NEEDS IN LYMPHATIC FILARIASIS

S. Jamal & S.P. Pani

"*There is no disease of which fuller or additional description does not remain to be written; there is no symptom as yet adequately described*" (John Ryle,1948).

Clinical manifestations of lymphatic filariasis are the obvious outcome of complex interactions of several underlying factors and processes related to the human host, filarial parasite and the environment. Hence, careful observation and study of clinical phenomena will help us: (a) to understand those interactions which influence the clinical consequence of infection from the time of inapparent infection to the development of irreversible clinical disease; (b) to design strategies to reduce morbidity and to control the disease effectively; and (c) to design the course of clinical management. An attempt is made below to identify the clinical issues which require further investigations and the attention of researchers.

Filarial aetiology of clinical manifestations:

Any understanding of the clinical consequence of infection necessitates a clear understanding of the terms 'infection' and 'disease'. The presence of the pathogen (in this case, the filaria parasite of any stage and sex) would mean infection (Jawetz *et al.*,1982). However, in practice, the detection of microfilaria is the only definite method presently available for the demonstration of infection. There can be several reasons why microfilaria may not be present or detected in an infected person (Beaver 1970 and Ottesen, 1989). It is also known that most microfilaria carriers (around 90%) are asymptomatic (Anonymous, 1985, 1990, Pani *et al*, 1989a, Kimura *et al*, 1985 and Pani *et al*, 1990a). These lead to difficulties in defining filarial disease. The classical manifestations of lymphatic filariasis are the most obvious clinical entities, and include acute adeno-lymphangitis, epididymo-orchitis, lymphoedema and hydrocele etc. (Partono, 1987, Ottesen, 1984, Turner, 1959 and Dissanaike, 1984). In epidemiological practice these manifestations (irrespective of patent microfilaraemia) are assumed to be of filarial origin in endemic areas. However, in a recent study (Dandapat *et al*, 1986) from a highly endemic area of India it was shown that filariasis was the definite cause of hydrocele only in 43% of cases, and that 27% of cases were of non-filarial origin. Similar findings have also been reported from Puerto Rico (Jachowski *et al*, 1962). Though filarial lymphoedema generally does not pose a

problem of clinical diagnosis, in as many as 14.0% and 20.4% of cases of Brugian and Bancroftian filariasis respectively, a history of previous episodic filarial fever was not elicited (VCRC unpublished data). Such cases, particularly in the early stages (not in obvious cases of elephantiasis), pose difficulty in the differential diagnosis of lymphoedema. Endemic non-filarial elephantiasis has been reported from Africa (Spooner and Davies, 1986) and such non-filarial elephantiasis was also reported from Rajasthan in India (Kalra, 1976). Detailed investigations have not been carried out. Apart from these, a host of other clinical entities have been reported to be caused by filarial infections (Patel, 1983, Chaturvedi *et al,* 1990, Muller *et al,* 1987, Seetharaman *et al,* 1988, Date *et al,* 1979, Singh *et al,* 1989, Agarwal *et al,* 1987, Yap *et al,* 1982, Devi and Bahuleyan, 1977, Thomas, 1978, Rao and Kumar, 1982 and Shah *et al,* 1982). Of these, glomurulonephritis, arthritis and endomyocardial fibrosis are probably of practical importance. Filarial lymphoedema predisposing one to lymphosarcoma also seems to be an important issue. The prevalence of this condition may be much higher than reported (Muller *et al,* 1987).

Defining the disease criteria is important from the point of view of clinical epidemiology (Dissanaike, 1979 and Wagesa *et al,* 1979). There were difficulties in the comparison of results between studies, and, this together with improper design seems to be responsible for the perception of geographical differences in clinical presentation in India (Pani *et al,* 1990b). Hence there is an urgent need to define and formulate criteria for clinical surveys.

Natural history of disease:

The natural history of lymphatic filariasis implies the sequence of events that occur from the time of infection to the development of clinical manifestations; early acute episodic manifestations to chronic disease. It is surprising that until 1986, there had been hardly any study on the natural history of this disease (Ottesen, 1987).

The sequence of events and the proportion of individuals who move from one clinical stage to another are not known. Whether all patients who develop acute manifestations will ultimately develop chronic disease is an important question. Are the chronic manifestations reversible in their early stages and if so in what proportion of cases does this occur naturally [redacted]?

The factors which decide the sequence of the progression from infection to different stages of clinical disease are unknown. This is an important area which is considered below.

The role of adult parasites and microfilaria and other factors such as immunity in the progression of disease is still not understood. Attempts to correlate clinical status with patent microfilaraemia have produced equivocal results. Though in some studies it has been shown that microfilaraemia influences the clinical outcome of infection (Kimura *et al,* 1985, Jordan, 1955, Marshall and Yasukawa, 1966, Raghavan, 1969, and Kessel, 1957), other studies did not support this (Pani *et al,* 1990a, Desowitz *et al,* 1976, Weller *et al,* 1982, and Raccurt *et al,* 1984). It has been widely accepted that the sequence of events from infection to disease is a function of the differential immunological response of individuals (Ottesen, 1984, Dissanaike, 1984 and Ottesen, 1980). Recent studies suggest that mF carriers who subsequently become amicrofilaraemic have a higher risk for progressing to chronic disease both in Bancroftian (Srividya *et al,* 1990) and Brugian filariasis (VCRC unpublished data). This could suggest that the progression of disease is a dynamic process from infection to disease. It may be hypothesized that mF carriers who subsequently become amicrofilaraemic have a very high risk of developing chronic disease, but the risk is modulated by the quality and quantity of the immune response. The major difficulty in understanding these processes is that studies made at a given point in time in the unusually prolonged natural history of the disease do not provide the answer. Therefore, longitudinal clinical, parasitological and immunological studies need to be carried out.

Acute episodic filarial fever attacks are the most important cause of loss of work from filariasis (Raghavan, 1969, Panicker and Sabesan, 1990 and VCRC Annual Report, 1987-88). Increased frequency of these attacks is associated with the progression of lymphoedema (VCRC unpublished data). It is not known what factors predispose or precipitate these attacks. Secondary bacterial infection, particularly with Beta heamolytic streptococci (Acton and Rao, 1929, Grace *et al,* 1932, Grace, 1943 and Evert *et al,* 1980), toxins liberated from the adult parasite (Chaterjee, 1965), immunological mechanisms (Piessens *et al,* 1980 and Ottesen *et al,* 1982), presence of septic focus elsewhere (Jamal, 1988) and repeated exposure to infective bites (Partono, 1987) have been suggested as the cause of such attacks. However, it has also been suggested that bacterial infection is unrelated to the occurrence of filarial fever (Weller, 1983). It is possible that some immuno-pathological changes precipitate the clinical attacks. These changes are triggered probably by several different mechanisms and the difference in clinical response depends upon the the nature and extent of the precipitating factor. Simultaneous clinical, bacteriological, parasitological and immunological investigations need to be undertaken to understand these interactions.

Differences between Bancroftian and Brugian filariasis. Recent findings suggest that the

progression of disease (particularly lymphoedema) is relatively slow in Brugian compared to Bancroftian filariasis (Anonymous, 1990 and Pani *et al,* 1989b). Evidence indicates differences in the mean duration of different grades of lymphoedema, the frequency of filarial fever attacks, the age specific patterns of lymphoedema grades and the degree of response to conservative therapy in the two forms of filariasis (VCRC unpublished data). However, prospective studies on the quality and quantity of toxins produced, antigen release and the immuno-pathological response evoked by the two parasites need to be investigated.

Effects of gender. The occurrence of disease in females is lower by a proportion of 0.39 compared to males in Bancroftian filariasis (Pani **et al**., 1990b), but not in the Brugian form (Turner, 1959 and Pani *et al,* 1990c). It is still not known what factors are responsible for the difference between the sexes. Relative difference in exposure to mosquito bites (Rajagopalan and Das, 1987) or difference in hormonal status (Sasa, 1976) may be important. It could also be due to the fact that the clinical consequence of infection in females is simply inapparent (Dissanaike, 1979 and Sri Vidya *et al,* 1990).

Anatomical abnormality in the lymphatics may predispose lymphoedema development. Lymphoscintigraphy has been advocated to study this problem (Dr.Wittie and Dr. Jamal, Personal communication), and to facilitate the surgical management of elephantiasis.

Issues related to clinical studies in populations (Clinical Epidemiology)

The need for defining clinical criteria has already been discussed above. The following are the other important issues.

Identification of clinical parameters which sensitively detect the changes that occur in a population after implementation of intervention measures is important. Difficulties in the epidemiological evaluation of vector control measures using parasitological data alone has been highlighted recently (Subramanian *et al,* 1989). It has been observed (March *et al,* 1960 and Krishnamoorthy *et al,* 1990) that clinical parameters were useful indicators of chemotherapeutic interventions, but their usefulness in vector control programmes is yet to be studied.

The time scale of disease. To understand the natural history of lymphatic filariasis as a population phenomenon over prolonged periods of time (decades), it is necessary to study the trend of disease prevalence in relation to infection (age specific profiles of microfilaraemia and dis-

ease) in different localities. A recent study on the long term changes on disease and microfilaria prevalence for a 50 year period in an Brugian filariasis area, provided an insight into the long term changes in the dynamics of infection and disease (Rajagopalan *et al,* 1989). Widely varying age specific patterns of infection and disease have been observed in different areas (Chand *et al,* 1960, Singh *et al,* 1963, Chand *et al,* 1960 and Srivastava and Prasad, 1969) and it will be worthwhile to study the present situation in these areas.

Indirect effects on mortality. There is a need to study if life expectancy of filarial patients is shorter compared to general population. Though it is known that death due to filariasis per se is rare, it might have an impact on the expectancy of life.

Issues related to the prevention or arrestment of disease progression:

Clinical criteria for deciding the management course: Development of lympho-nodo-venous surgery (Jamal, 1981) has formed a landmark in the advanced management of filarial lymphoedema. However, there is an urgent need to train young surgeons all over India in this procedure, and the longterm effectiveness of this in different hands needs to be evaluated. Conservative management has also produced good results in Brugian (Pani *et al,* 1989b, Partono, 1985 and WHO, 1985) and less so in Bancroftian lymphoedema (VCRC Annual Report, 1989 and Kar, S.K. personal communication). However, 15% of Brugian and 38% of Bancroftian filariasis cases show increased oedema volume in spite of therapy, and probably will respond only to surgical intervention. Hence it is necessary to define what factors (such as frequency of filarial fever, degree and duration of oedema) decide the outcome of conservative therapy. These data together with the results of investigations such as lymphoscintigraphy which is a non-invasive technique (Witte *et al,* 1988 and Jenkins *et al,* 1985) or lymphangiography (Tan *et al,* 1985 and Cohen *et al,* 1961) may form the basis for defining the criteria for deciding the course of management. Limphoscintigraphy is promising in detection of cases who have a risk of developing lymphoedema (particularly mF carriers) in their preclinical stages. Using portable detectors it may be possible to carry out community studies to detect the population at risk. This will also be useful in studying the anatomy and physiology of lymphatics in relation to filariasis disease at population level.

Chemotherapy and disease. It is necessary to study the role of other anthelmintics such as mebendazole, levamisole and albendazole in modulating the process of infection and disease. Mebendazole has been reported to produce clinical cure in calabar swellings (Van Hoegaerden *et al,* 1986). There is also a need for the scientific evaluation of modern physiotherapeutic

measures such as short wave diathermy and application of ferradic current with and without drugs.

DEC therapy has been shown to produce occular manifestations in onchocerciasis leading to blindness (Ottesen, 1985 and Duke and Thylefors, 1986), however, there is no conclusive evidence that longterm adverse clinical effects are also produced in lymphatic filariasis. It is also known that in hitherto asymptomatic carriers, DEC therapy can result in epididymo-orchitis or lymphoedema (Ottesen, 1985).

Secondary bacterial and fungal infections are known to complicate some of the lymphoedema cases (9.6% in bancroftian filariasis in Pondicherry: VCRC unpublished data). There is a need to study the nature and extent of these and the influence of these on the clinical course of lymphoedema.

There are several unresolved issues in the understanding of the clinical consequence of infection and the factors affecting the outcome. The above discussion is by no means exhaustive since there are many other issues of interest, such as the difference in occurrence of Tropical Pulmonary Eosinophilia (TPE) between different groups of populations (Dr. Kumaraswami, personal communication). The areas of priority are those related to understanding the natural history of lymphatic filariasis and the management of lymphoedema as part of community control programmes.

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5. SOCIOECONOMIC PERSPECTIVES

K.N.Panicker & S.Sabesan

The socioeconomic component is perhaps the most neglected aspect of lymphatic filariasis research. Even though one third of the world's population at risk of the disease live in India (WHO, 1984; Anonymous, 1989), this disease has not received its due attention because the socioeconomic impact is underestimated and largely unrecognised. There are but few reports on this aspect (Jain, *et al.*, 1986; Sunny, *et al.*, 1986; Sunny, *et al.*, 1988; Hyma, *et al.*, 1989). New research in this field is essential for three main reasons: (i) in order to quantify the economic and social impact of the disease for policy makers; (ii) to devise methods to study the community with regard to knowledge, attitude, practice and projudice in relation to the causation and control of disease and (iii) to develop and implement a control strategy acceptable to the community and therefore sustainable. The socioeconomic research needs with particular reference to India are briefly outlined below.

The economic and social impact of filariasis: India has over 22 million microfilaria carriers and 18 million diseased persons (Sharma, *et al.*, 1983). An even larger proportion suffer from repeated attacks of filarial fever, which results in loss of work and therefore economic production (Raghavan, 1969). A recent estimate of the frequency and duration of these episodes and the consequent economic loss in productivity alone is shown in Table 1 (VCRC unpublished data). Although these are significant underestimates (e.g. they do not include the cost of therapy and hospitalization) they provide some indication of the considerable extent of the loss. Substantial work was carried out in the early part of this century on the socioeconomic impact of malaria on India (Sinton, 1935a, 1935b and 1936), and similar data should now be generated for filariasis.

The social impact of the disease is least understood. Many filariasis patients remain unmarried because of social rejection. Social and psychological stresses exist in the interaction of filariasis patient with their own family members and others in the community. These social health impacts of the disease have not been studied scientifically. Documentation of these will not only enable one to understand the extent of the problem but also help to devise means to overcome them.

Filariasis and the community: Many health programmes fail to make an impact since the strategy does not assign any role for the community in implementation. India being a vast country, there exists a variety of communities at different levels of psychological and social growth. Rural and urban communities, for example, cannot be expected to behave in the same manner. A thorough understanding of the knowledge, attitude and practices of the local community is very important for the successful implementation of any programme. The community should be made aware of the filariasis problem and the methods for its control. The community then has to accept the methods and to involve itself in the implementation process. Finally, such activities must induce continued interest so as to sustain the activity. This is obviously a slow process, and research in this area is difficult. Furthermore, there are no fixed criteria for evaluating community participation. Uniform criteria need to be developed so that comparison of the extent of community participation obtained in different localities will be possible. It is necessary to define the term participation itself.

Community participation is essential both for vector control and chemotherapy. Several methods have been evolved for generating active community involvement in vector control projects carried out by the Vector Control Research Centre (VCRC). Income generating schemes have been found useful in achieving sustained participation both for malaria and filariasis control programmes (Rajagopalan and Panicker, 1981 and 1986; Rajagopalan *et al.*, 1987; Ambili Kumar, *et al.*, 1989; Rajagopalan, *et al.*, 1990). The Centre is implementing a programme in Shertallai area where massive community participation has been achieved for Brugian filariasis control. A mass movement has been initiated under the filariasis control movement (FILCO) with a membership of 16,000 volunteers. This organisation is involved in health education, physical removal of hydrophytes, pisciculture, alternative manure production, and other factors contributing to vector control. Presently the FILCO has also undertaken the job of parasitological screening and delivering chemotherapy by organising Filariasis Detection and Treatment Centres in different localities under the technical guidance of VCRC.

Apart from DEC, the phase I trial of Ivermectin, a promising antifilarial drug, is nearing its completion. This is expected to undergo community trial in the future. With the enriched experience of community participation for vector control and DEC therapy, Vector Control Research Centre will be able to undertake such trials for Ivermectin as well.

Socioeconomic factors in development and implementation of control strategy: Development of an effective disease control strategy is only one step in the lengthy process that culminates

in its application. The final success of the strategy depends on community acceptance. Hence the strategy developed should be simple, feasible, easily acceptable. Local factors relating to the community need to be given due emphasis in this process.

Before formulating strategies, therefore we need to study the response of the community by pilot trials. Many gaps exist between the researchers and the health planners/ implementors in the application of technologies. Methods have to be evolved for developing coordination between these and related agencies for appropriate community participation.

In the formulation of policies for national programmes, it becomes highly important to evaluate the cost-effectiveness of different control measures for filariasis. Though methods for cost-effectiveness analyses have been developed, standardized and used for the evaluation of malaria programmes in India (Ramaiah, 1980) no such methods have been evolved for evaluating filariasis programmes. Development of comprehensive economic evaluation method for control programmes, is necessary for comparison of the results of different studies.

The preliminary evaluation of the Brugian filariasis control programme of VCRC at Shertallai indicates that the programme is extremely cost-effective. The evaluation has also revealed that, while the budget grant for the project was only Rs.3,700,000 for three years, the programme helped to generate a net profit to the community of about Rs.6,400,000 through composite fish culture, accounting for nearly 2 times the total budget grant (Report of the Mid-term cost benefit evaluation of Shertallai project submitted to the SA to Prime Minister by the School of Management, Pondicherry University). Cost analysis of the integrated vector management programme in Pondicherry has also shown that it is possible to maintain effective vector control with a per capita expenditure of Rs.6.4 per year (Rajagopalan and Das, 1987).

This brief review indicates that the socioeconomic component is the most neglected area in lymphatic filariasis research, and that there is an urgent need to develop methods for such research. The priority areas are: assessing the socioeconomic impact of the disease; defining community participation; and developing methods for evaluation of participation. The role of the individual and the community has to be specified.

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Table : 1

Crude estimate of Economic loss due to Bancroftian filariasis in Pondicherry and Malayan filariasis in Shertallai.

		Bancroftian filariasis	Malayan filariasis
a.	Total Population.....	3,72,000	4,35,000
b.	Number of working population (20-58 yrs. only)*...	1,61,076	1,88,355
c.	Disease rate in working population.....	11.51%	9.57%
d.	Total number of diseased persons in working age..	18,540	18,025
e.	Frequency of acute attacks resulting in loss/year...	4.47	2.20
f.	Duration of each attack in days.....	3.90	4.05
g.	No. of man days lost per case in day (exf).....	17.43	8.91
h.	otal man days lost/year (dxg).....	3,23,205	1,60,603
i.	Minimum daily wage (accepted by Govt.) in Rs.....	24.00	24.00
j.	Economic loss in a year (in Rs.) (hxi).....	77,56,913	38,54,466

* = Calculated as per age distribution, source Registrar General of India.

6. CHEMOTHERAPY OF LYMPHATIC FILARIASIS

V.Kumaraswami

There are several problems that hamper the development of an effective chemotherapeutic strategy for lymphatic filariasis. The goals of chemotherapy are not clearly defined; drugs which are clearly microfilaricidal are expected to be macrofilaricidal and there is considerable difficulty in deciding what is best for an individual as opposed to what is good for the community. In addition, unanswered questions regarding infection and uncertainity of the duration of the prepatent period make assessment of chemotherapeutic regimens difficult. Furthermore, the absence of markers (parasitological, immunological or molecular biological) that indicate an end point of treatment are lacking. Human attitudes, be they those of the individual, communities or more importantly health professionals, which influence compliance to various antifilarial regimens have also varied and thus influenced the outcome of control measures.

Currently two drugs are available for use as chemotherapeutic agents in lymphatic filariasis - diethylcarbamazine (DEC) and ivermectin.

DEC: DEC has been in use for over 40 years now. Several studies have been conducted all over the world and millions of patients have received the drug. Yet there is no consensus over the optimal dosing scheme that is best for lymphatic filariasis. The drug is known to transiently eradicate microfilaraemia, act partially on the adults and has little or no effect in clinical disease. The greatest barrier to its widespread use, as in mass chemotherapy programmes, has been its reactogenicity in populations. Further, even in a "standard" course it needs to be given for at least two weeks. The last two factors have made it a very unpopular drug in mass campaigns.

However, DEC cannot be dismissed as a drug unworthy of use in the management of lymphatic filariasis. Recent rexamination of the literature accumulated over the last 40 years of DEC usage has helped to redefine a role for DEC. Some of the important lessons learnt are:

1. High total doses are more effective than smaller (conventional) doses.

2. Spaced dosage regimens produce better results than single treatment regimens.

3. Chronic dosing as occurs with DEC medicated salt, appears to be an effective approach.

4. The drug appears to have a macrofilaricidal effect as evidenced by (a) histological findings in humans and experimental animals, (b) nodule formation which is indicative of death of adult worms, (c) sustained suppression of microfilaraemia, (d) reversal of clinical disease such as tropical pulmonary eosinophilia (TPE) and some forms of early lymphoedema and (e) by immunological changes post-treatment.

One approach which has consistently shown good results as a treatment strategy is based on the use of DEC as medicated salt. Since prolonged exposure to DEC does not result in the development of resistance to the drug and as the drug is stable on heating, nontoxic and tasteless it can easily be added to common salt. Several studies have demonstrated that side effects are minimal and costs are low when populations are treated with DEC medicated salt. This approach also assures a prolonged exposure to the drug.

Despite the plethora of studies which have been conducted with DEC there is no "optimal dosing" regimen either for the individual or communities.

Ivermectin: Ivermectin, a semi-synthetic, has recently emerged as the drug of choice in the management of onchocerciasis.

Nearly 200 patients with bancroftian filariasis have been treated with single doses of ivermectin using doses ranging from 20 to 400 mcg/kg. In all these patients microfilaraemia was rapidly abolished but returned to 10 to 20% of the pre-treatment levels by six months. In some studies doses of 100 mcg/kg or greater were found to be marginally superior in efficacy to 50 mcg/kg. In other studies no significant differences in efficacy were noted among the doses but the 20 mcg/kg dose, with equivalent efficacy, caused significantly fewer adverse experiences.

In a double blind study the efficacy and side effects of ivermectin at two dosage levels (1 or 6 mg capsules corresponding to approximately 20 and 120 mcg/kg) were compared with that of the standard drug DEC. Forty patients received 51 courses of treatment; 14 received DEC, 13 ivermectin (6 mg), 13 ivermectin (1mg) and 11 placebo. The effect of ivermectin was identical in the initial dose-finding studies. Microfilaraemia cleared in all patients within the first

two weeks and began to reappear at one and three months. Although both ivermectin doses rapidly cleared microfilaraemia their ability to suppress microfilaraemia at six months was inferior to that of DEC. Importantly, there was no difference, either qualitatively or quantitatively, in the side reactions that occurred in both treatment groups.

In these studies several signs and symptoms were assessed and scored, and total adverse reaction scores were generated which were then utilised to compare regimens. Two important findings emerged from these observations (a) "reactions" were dependent on pretreatment microfilarial densities, (b) lower doses of ivermectin tended to produce fewer reactions. Based on the latter observation a study was carried out using very low doses of ivermectin (10 mcg/kg). This study clearly showed that a 10 mcg/kg dose was just effective as the other doses tested with the added advantage of being less reactogenic.

Thus, ivermectin has been shown to be superior to DEC in rapidly clearing microfilaraemia and just as effective as DEC in suppressing microfilaraemia at one and three months. However DEC was superior in suppressing microfilaraemia at 6 months. The "reactions" or side effects were essentially similar to those that occurred with DEC treatment and were generally less in the lower dosage groups. Ivermectin's superiority lies in the convenience of single dose administration.

Further trials to compare the effects of a single dose of DEC and split doses of ivermectin are being planned at several centres.

7. TRANSMISSION DYNAMICS OF LYMPHATIC FILARIASIS

B.T.Grenfell

Compared to other areas of parasite epidemiology, theoretical approaches to the population biology of lymphatic filariasis have been relatively undeveloped. This situation arises mainly from the practical complexities of assessing infection and disease status in human populations (Sasa, 1967), and emphasises the importance of quantitative epidemiological studies, based on detailed data sets (Vanamail et al., 1989; Srividya et al., 1990). Here, we review previous and current progress in the construction of mathematical models for lymphatic filariasis transmission and discuss future directions for work in this area.

Progress in quantifying the transmission dynamics of filariasis can be grouped under two broad headings

Catalytic infection models, which consider the proportional age-distribution of an endemic infection in a human population, in terms of the age-specific rates of gain and loss of parasites. The seminal study here is by Hairston and Jachowski (1968), although a number of other workers have adopted this approach (Hayashi, 1962; Indrayan et al., 1970; Vanamail et al., 1989; Bundy et al., 1990; Srividya et al., 1990). Recently, work at the VCRC has led to a new model, which accurately represents the age distribution of infection, and its relationship with the pattern of chronic disease (Vanamail et al., 1989; Srividya et al., 1990). As discussed below, this formulation provides a unified comparative descriptor of filariasis data sets from a variety of endemic areas (Bundy et al., 1990).

Parasite intensity models, in which the number of parasites per host is considered explicitly, have concentrated on the infection dynamics of the vector host (Pichon, 1974; Pichon et al., 1980), and the overall success of transmission through the parasite's life cycle (Beye and Gurian, 1960; Hairston and De Meillon, 1968). Recently, Das et al. (1990) have proposed a statistical model for the frequency distribution of microfilarial intensity in human populations, which provides evidence for density-dependent (probably immunological) influences

on the infection pattern.

In the following section, we focus on ongoing work by the VCRC which addresses the central epidemiological question of the relationship between infection and morbidity in humans. The entomological aspects of transmission are considered in more detail by Das in Chapter 2.

A central problem in filariasis epidemiology is the inability to quantify the adult worm burden of infected humans. Despite this, considerable progress in understanding the dynamics of infection and disease can be made by analysis of the VCRC's uniquely detailed microfilarial and clinical surveys for bancroftian filariasis. As discussed below, these analyses have allowed (a) the construction of a catalytic model for the age prevalence of microfilaraemia in humans, (b) the use of this formulation in providing a successful model from the relationship between infection and disease status, and (c) the development of a statistical model for the relationship between mF prevalence and intensity.

The mF age-prevalence model:

As described above, reversible catalytic infection models require estimates of both the rate of gain and loss of infection as functions of age (Hairston and Jachowski, 1968). Ideally, such estimates should be based upon a longitudinal study, which considers how the mF status of a cohort of individuals changes through time. As described by Vanamail et al. (1989), an ideal data set for this purpose is provided by the VCRC data base on bancroftian filariasis.

Vanamail et al. (1989) used a reversible catalytic model to estimate the age-specific rates of gain and loss of *Wuchereria bancrofti* infection from data collected during the VCRC control programme in Pondicherry. The data describe the infection status in 1981 and 1986 of two cohorts of individuals, one living in an area where vector reduction had been achieved, and the other in a comparable endemic area. The rate of loss of infection in the absence of reinfection was estimated for the cohort in the control area, and the rate of gain of infection by the cohort in the endemic area calculated by substitution in the model. The mean expected life span of patent infection was estimated to be 4-5 years, and the instantaneous rate of loss of infection was shown to be independent of age. The rate of gain of infection exhibits a convex age-profile, peaking in the 16-20 year age-class. The reduced rate of gain in adults is largely attributable to the increasing proportion of potentially resistant individuals with clinical disease. The results suggest that the age distribution of bancroftian filariasis is primarily determined by age-dependency in the rate of acquisition of infection.

The relationship between infection and disease:

Most previous studies have emphasized the complexities of the relationship between infection and disease in lymphatic filariasis. By contrast, Srividya et al. (1990) and Bundy et al. (1990) use simple mathematical models to clarify the disease-morbidity relationship. Srividya et al. (1990) examine the relationship between the dynamics of *Wuchereria bancrofti* infection and the development of chronic lymphatic disease. The VCRC's Pondicherry data set is used to estimate the age-specific proportion of the endemic population, which converted from microfilaria positive to amicrofilaraemic, and is assumed to be at risk of disease. For men, but not women, the age-prevalence profile of the estimated population "at risk" is shown to correspond closely to the observed age-prevalence of chronic lymphatic disease in the same community. For both sexes, and independent of age, approximately 11% of the population at risk eventually develop lymphoedema. These observations suggest that filariasis-endemic populations consist of those individuals who remain amicrofilaraemic and asymptomatic, and those who progress through the sequence: uninfected microfilaraemic, amicrofilaraemic to develop irreversible obstructive lymphatic pathology.

Bundy et al. (1990) have since extended this study in a comparison of the Pondicherry situation (where infection rate and therefore mF prevalence are comparatively low) with regions (such as Tanzania) with higher infection rate and prevalence. Unlike the Pondicherry results, the Tanzania analysis shows that a significant proportion of clinically diseased individuals are positive for mF. This leads to a modification of the basic model of Srividya et al. (1990) to allow for the reinfection of diseased individuals. The resulting formulation successfully captures the epidemiological picture in different regions, indicating the generality of the method.

mF prevalence and intensity distribution:

In a further analysis of the Pondicherry data, Das et al. (1990) examine the effects of host age and sex on the frequency distribution of *Wuchereria bancrofti* infections in the human host. Microfilarial counts from a large data base on the epidemiology of bancroftian filariasis in Pondicherry are analysed. Frequency distributions of microfilarial counts divided by age are successfully described by zero-truncated negative binomial distributions, fitted by maximum likelihood. Parameter estimates from the fits indicate a significant trend of decreasing over-dispersion with age in the distributions above age 10: this pattern provides indirect evidence for the operation of density dependent constraints on microfilarial intensity. The analysis also

provides estimates of the proportion of mF positive individuals who are identified as negative due to sampling errors (around 5% of the total negatives). This allows the construction of corrected mF age prevalence curves, which indicate that the observed prevalence may underestimate the true figures by between 25% and 100%.

The above analyses constitute essential steps in the construction of a model for the overall transmission dynamics of lymphatic filariasis. The model proposed by Srividya et al. (1990) provides a powerful and general epidemiological tool for examining various hypotheses about the relationship between infection and disease in lymphatic filariasis. However, the description which it generates is, at this stage, a phenomenological one only; further immunological studies are required to clarify the *mechanism* of the disease process.

One objection to the use of prevalence models is that they can not be used to quantify the distribution of mF intensity in human blood and therefore the potential infection pressure on the vector. However, the model proposed by Das et al. (1990) provides a potential solution to this problem by establishing a quantitative link between mF prevalence and intensity as a function of human host age. Furthermore, the distribution provides evidence of acquired immunity to infection and indicates fruitful directions for immunological research.

Finally it is important to note that the catalytic models described are steady state models, which do not take account of temporal changes in infection and disease. Given that control interventions are based on inducing changes in infection levels any overall transmission model should be a dynamic formulation which takes temporal changes into account.

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8. OPERATIONAL RESEARCH FOR CONTROL

M.V.V.L. Narasimham

In the planning of control methodology for filariasis, a feasible and cost effective strategy with adequate resources in terms of finance, trained man-power and material is the primary requisite, along with the monitoring and evaluation components and concurrent operational research on impact of control operation on transmission, and the resultant reduction in morbidity.

Areas needing operational research on a priority basis are enumerated below:

1. Assessment of the magnitude of the problem (quantification):

At present, point or period prevalence and incidence by sample surveys for microfilaraemia and disease are being adopted and extrapolated to larger populations in the same eco-epidemiological areas. In addition, institutional data are also being utilised as supportive data.

A series of parameters has yet to be developed to assess the transmission dynamics.

2. Trends of transmission and forecasting the impact of control methodologies:

Currently, filariasis surveys are carried out measuring simple parasitological, entomological and clinical parameters which are based on data collected before and after the start of control measures. There are at present no parameters for ecological or environmental changes. A "transmission intensity index", incorporating different vectorial and clinico-parasitological parameters, should be developed to assess the performance of control programmes.

VCRC, ICMR, Pondicherry is developing a model in the urban situation, where integrated vector control methods have been adopted, to indicate the trend of transmission and also for forecasting how the infection can be brought to near zero level. Applications of the model to different control measures and areas would help determine the utility and reliability of this model.

3. Environmental Factors:

There is no model for studying the relationships between endemicity levels, vector populations and environmental factors. This is relevant since there has been continuous environmental degradation in urban areas and many developmental activities adversely effect health.

4. Monitoring and evaluation:

4.1. Studies on alternative control methods, such as anti-larval, anti-parasitic, habitat modification, need to be studied in relation to their efficacy and their effects on human and animal life, particularly where ecological changes are taking place.

4.2. Cost-effectiveness studies of the continuous use of larvicides over a period of years, the application of environmental management methods, and the use of larvivorous fish and other biological control agents need standardized protocols.

4.3. A management information system for the impact of programmes is required.

4.4. Operational research on the managerial aspects of control programmes requires attention to establish, for example, the extent to which the planned aims are being achieved, or not achieved, through the knowledge, and attitudes and managerial skills of different categories of staff in the programmes.

5. Health Economics:

The productivity lost to the community as a result of filariasis, and the economic loss to the individual and family, either directly through expenditure or indirectly through loss of working time, requires estimation in order to present a better assessment of the extent of the problem to the policy makers.

6. Studies on human behaviour:

The perception and understanding of the community with regard to the cause of filariasis and the measures required for prevention and treatment need study. It is also necessary to establish the attitude of communities towards control programmes and their capability and willingness to cooperate with the health staff.

7. Indigenous Drugs:

In India, different systems of medicine are in practice, such as Allopathy, Ayurvedic, Homeopathy, Unani and Sidda. Field trials are being carried out to measure the efficacy of indigenous drugs for clearance of mf and for the treatment of disease manifestations. There may be indigenous drugs in other countries which need screening to establish their potential efficacy in control programmes.

9. CONTROL PERSPECTIVES

P.K.Rajagopalan and P.K.Das

Lymphatic filariasis is a major public health problem and with the present rate of unplanned urban growth the situation may worsen further if suitable measures are not undertaken. It has been suggested that filariasis, caused by *Wuchereria bancrofti* and *Brugia malayi*, can be easily controlled by the combination of chemotherapy (DEC) and vector control. However, the experience of over 30 years of control efforts under the National Programme in India and elsewhere does not support this view. It is also suggested that China has successfully controlled filariasis by DEC therapy; such reports contradict the fact that India, China, Indonesia still contribute more than two thirds of all lymphatic filaria cases in the world. Vector control combined with chemotherapy can indeed break transmission, but it is difficult to sustain this for prolonged periods due to financial and administrative constraints.

The epidemiology of filarial disease is such that intensified control programmes should continue in an area for at least 15 years (assuming the life span of the adult worm as 15 years). However, most control programmes function for a shorter duration and after a few years these programmes generally became non functional. If surveillance and treatment, or mass chemotherapy through medicated salt, were carried out for 40 years, one would have eliminated the disease, if not infection.

Our experience shows that complacency replaces efficiency in most programmes, and slowly disease and infections re-establish. The main reason is that a majority of mf carriers are asymptomatic, and asymptomatic people typically have low compliance. This problem has been further aggravated by concern over AIDS. Therefore detecting mf carriers and their treatment has to be replaced with mass drug therapy, ideally through a medicated salt programme. Wherever possible, vector control should be undertaken by civic bodies with community participation.

Many studies have shown that DEC medicated salt has been very successful in bringing down mf rates in the population. Since these programmes were carried out only on a small scale in space and time the disease has always re-established itself after reversion to the original strategy.

A DEC medicated salt programme undertaken at a national level for at least 15 years throughout the filarial endemic belt may be able to eliminate the parasite. Such a programme deserves evaluation for its effect on transmission and disease.

Recent developments in lymphangiography and lymphoscintigraphy can be of great help in the surgical management of patients. This is being done only on a limited scale in a few medical colleges, and it would serve a great humanitarian cause if the facilities for such surgical interventions were established in all district hospitals in the endemic belt. ICMR can play a major role in establishing such facilities in a phased manner. This would include training of surgeons and providing infrastructural facilities.

The present methods for controlling *C. quinquefasciatus* are effective enough to control the vector to a level which can satisfy people by avoiding the mosquito nuisance, but will not interrupt transmission without the simultaneous use of chemotherapy, as demonstrated in Pondicherry. Consideration needs to be given, however, to the following logistic and operational difficulties.

The present strategy of weekly application of larvicide is not sustainable. The efficacy of seasonal control of filariasis vector on transmission need to be evaluated. The feasibility of slow release formulations for vector control in large scale operations needs to be tested. This will not only reduce the frequency of application but also the cost of buying and maintaining spraying equipment.

An additional sociological problem is that people do not want to be seen carrying spraying equipment because such jobs are not considered respectable. As a result, the sprayman will dispose of the insecticide and return to the office without spraying the breeding habitat. Slow release briquettes can overcome this problem. Slow release formulations can also be applied by the community.

There is little fundamentally wrong with the present methods of control except that they require intense and sustained effort which is difficult to maintain. As a result, these methods are not the ultimate solution for a complex problem like filariasis and research should continue to overcome these difficulties. The fields in which research is required are:

a) The search for better chemotherapeutic agents and novel control methods should continue. Synthesis of alternative compounds and their screening for macrofilariacidal activity should be intensified. Design of new classes of compounds should be based on the biology of the parasite and the host-parasite interaction.

b) New biocides are useful in controlling vector population but these agents are not available for use. Their efficacy has yet to be proved in large scale field trials. Efforts should be made to make available such products which can be applied by the community.

c) One of the strong points of the filariasis vector is its breeding potential. Without reducing breeding potential one can not control this species in the long term. Apart from environmental sanitation, development of oviposition attractants should be given priority. If a suitable attractant is developed, it can be used not only for control but also for evaluation of vector populations.

d) Reduction of man-vector contact by various means (e.g. clothing pattern, use of fan, mosquito-coils, bednets, mats) is known to reduce the transmission potential. But most of these are neither acceptable nor affordable to the majority of the community. Therefore tailoring these methods to suit the cultural practices of the people and bringing down the cost to an affordable level, deserves active consideration. For example, while impregnated nets are effective in protecting people from mosquito bites under tropical conditions sleeping under a net is often unacceptable. The impregnation of curtains may be a more attractive alternative.

Controlling mosquitoes like *Culex quinquefasciatus,* which has co-evolved with humans, is not going to be an easy task. Efforts to control this species have been counterproductive, and it has been suggested that the species is more ingenious than man. Research on alternative methods of control should be a continuous process.

10. THE ROLE OF WHO/TDR IN FILARIASIS RESEARCH

C.P. Ramachandran

Dr. C.P. Ramachandran, Secretary, Steering Committee Filariasis, Special Programme for Research and Training in Tropical Diseases gave a brief presentation on the objectives and strategies of the Steering Committee on enhancing research in lymphatic filariasis. He explained that there are three main areas in which TDR is actively promoting research.

1. Drug development and chemotherapy.

2. Immuno-diagnostics including recombinant technology, and

3. Epidemiology and Field Research.

New tools developed in these areas for prevention, diagnosis, treatment and control of lymphatic filariasis must be effective, appropriate and affordable for use in the National and Regional context. Several examples of TDR sponsored research conducted in India were presented and the importance of continuation of these programmes was stressed. Novel methods for treatment and diagnosis of filarial disease must be developed urgently to control the disease which is affecting over 80 million people in the world. He then went on to give a synopsis of the current objectives of the Steering Committee, as follows:

Objectives:

1. To discover and develop new filaricides especially macrofilaricides.

2. To improve and expand on the utility of existing antifilarials, and establish the efficacy, tolerability and field use strategy for novel antifilarial drugs.

3. To provide practical immuno-assays for the detection of prepatent infections, improvements in diagnosis and monitoring of drug-related effects on parasites.

4. To define host-response contributions in the pathogenesis of filariasis and in the generation of adverse drug-related experiences post-treatment so as to identify risk factors of epidemiological and clinical utility.

5. To determine the role of host protective responses in filarial infections and assess the prospects for immunoprophylaxis.

6. To improve scope and efficacy of methods of filarial disease control.

7. To provide convenient, sensitive, objective methods for detection and identification of parasites and parasite variants (forms) in biological samples, especially vectors.

11. FUTURE RESEARCH NEEDS: INTRODUCTION TO THE RECOMMENDATIONS

The following six chapters summarise recommendations for future research in India into lymphatic filariasis. The research proposed is intended to contribute to the overall aim of reducing the morbidity due to lymphatic filariasis by defining procedures which are cost-effective, sustainable and appropriate to the Indian context.

Socioeconomic research was considered to be a particularly neglected area, yet one which is of considerable importance. Data on the social and economic cost of lymphatic filariasis are urgently needed to rectify the under-recognition of the disease by Health Policy Makers.

In the area of **Control**, research is required to assist the Policy Maker and programme manager in identifying the most cost-effective and appropriate mix of control strategies. A quantitative framework, such as a mathematical model, was seen as particularly important in this context, provided that it was combined with increased understanding of practical procedures of implementation: identifying optimal control approaches is only worthwhile if the measures can be implemented, while effective implementation is only useful if the correct control approach has been selected.

Epidemiological Research has progressed considerably in recent years, and there is now clear understanding of patterns of infection at a few specific foci. This work requires extension to a broader range of geographical areas, and the refinement of epidemiological and clinical measures in the light of the improved understanding.

Immunological Research has achieved much in explaining the immunopathology of lymphatic filariasis, but much remains to be done. There is a major need for increasing laboratory capacity in this area, and for multidisciplinary studies combining epidemiological, clinical and immunological procedures.

The major impediment to progress in **Clinical Research** is a lack of consensus as to what constitutes the disease manifestations of lymphatic filariasis. Considerable progress has been made in developing clinical tools (e.g. lymphoscintography) and these should receive wider application.

Research in **Transmission Dynamics** has made considerable progress and may soon provide

a preliminary model. Adaptation of this model for the preliminary assessment of the cost-effectiveness of control procedures is an important next step.

All these recommendations depend on the existence of a skill and resource base within India. Continuity and improvement of training opportunities are therefore essential prerequisites. Training must be maintained and expanded in the areas of obvious direct relevance to research and control of lymphatic filariasis: medical entomology, epidemiology and immunology. In addition, there is a need for inclusion of relevant training in areas, such as civil engineering, sociology and economics, which have not traditionally been considered relevant to the control of vector borne disease.

12. RECOMMENDATIONS FOR SOCIOECONOMIC RESEARCH

1. **Social and Economic Impact to be defined and clarified for policy makers.** Important aspects which are currently under-recognised include the effects of elephantiasis on: employment and career prospects; educational opportunities; marriage and family cohesion. The mental health consequences of ostracisation, rejection and stigmatisation should be assessed. The specific costs of the persistence of disease, that is the cost of **inaction**, should be accurately estimated for different endemic areas. These costs will include: labour losses; opportunity costs; hospitalisation and treatment.

2. **The opportunities for promoting community involvement and community empowerment to be assessed.** This requires the conduct of Knowledge, Attitude, Practice and Prejudice (KAPP) studies in a wide range of endemic communities. The need to identify myths in order to develop demystification educational packages is particularly stressed. These studies should also examine the opportunities for cost retrieval and income generation.

3. **The interaction between community literacy and health education to be assessed**. Studies should be conducted in areas of high literacy (e.g. Kerala) and low literacy levels, and also in areas of varying educational level.

4. **Carry out a detailed assessment of the economic and social impact of brugian (and later bancroftian) filariasis in areas under study by VCRC.** The side result of this study will be the development of a protocol for making such assessments that can be utilized in many places around the filarial endemic world. Some definition of the **impact** of the infection will be required to mobilize the support of governmental authorities everywhere, the development of such a protocol would be a tremendous contribution to the overall programme for filariasis control worldwide.

5. **Much epidemiological research proceeds in an economic vacuum, in that it does not consider the costs (and therefore the economic feasibility) of control programmes.** The Seminar therefore recommends that socio-economic studies be initiated to quantify the costs of current and proposed filariasis control programmes (and in particular IVM and various strategies for chemotherapy), as well as the benefits (in terms of the alleviation of suffering and other socio-economic indices), achieved by given reductions in morbidity.

13. RECOMMENDATIONS FOR CONTROL RESEARCH

13.1. OPERATIONAL ASPECTS.

1. **There is a need for more detailed information on the current distribution of infection and disease in India.** Attempts should be made to standardise the quality of data.

2. **Techniques for forecasting the impact of control programmes are required in order to assist the design of locally appropriate control strategies.** Such a procedure should be based on measurable parameters of the local vectorial, clinical and parasitological situation. It should also be able to account for a range of interventions (eg. DEC, medicated salt, IVM etc).

3. **Comparison of the cost-effectiveness of different control interventions or different mixes of interventions should continue.** Particular attention should be given to the role of engineering interventions.

4. **Methods of applying control methodologies in rural areas require assessment.** This will have to account both for those areas with good primary health care systems, as well as those, which lack an appropriate health infrastructure.

5. **Managerial aspects of programmes crucial to implementation.** Information on the KAPP of health professionals and the community is necessary. This information can be used for the training and motivation of health workers and community leaders.

13.2. CONTROL TOOLS.

Basic Science:

1. Although DEC has been in use for forty years it is still not clear how it acts. The mode of action of DEC and Ivermectin needs to be studied.

2. In order to study the efficacy of a drug we need to measure its level at the site of residence. In lymphatic filariasis we measure blood levels while the parasite lives in the lymphatic system. Studies should be done to estimate **drug levels** in the lymph.

3. The interaction between the drugs and the immune system should be explored since microfilarial clearance is in part immune mediated.

4. Assays (immunological and molecular biology-probes) need to be developed to identify end points of treatment (i.e. killing of adult worms).

Clinical:

5. Since both DEC and Ivermectin have specific individual advantages, it may be advantageous to explore combination therapies.

6. The effect of DEC and Ivermectin on the clinical forms of the disease should be studied.

7. Efforts must be made to minimise reactions post-treatment, by altering treatment schedules or concomitant use of anti-inflammatory drugs and/or antihistamine.

8. It is desirable to design studies that will examine the usefulness of DEC and Ivermectin as prophylactic agents.

Operational:

9. Mass chemotherapy programmes based on large scale field trials using DEC should be designed to obtain information regarding the effect of treatment interval on transmission.

10. Combination of mass chemotherapy and selective chemotherapy needs to be reviewed. The relationship of development of reactions with one single dose has to be quantified. This may help in identifying the infected individuals in mass chemotherapy programmes. These individuals can be treated with a full course of DEC and this may help in reducing parasite load at a faster rate.

11. DEC medicated salt should be evaluated in multicentre trials for its efficacy and prophylactic value.

12. Identification of optimal dosage regiments for DEC for standardised treatment of filariasis is required.

13. Due to practical difficulties in the implementation of sanitation, public health engineering and management procedures, efforts towards the development of microbial biocides and other biological control agents should be continued.

14. RECOMMENDATIONS FOR EPIDEMIOLOGICAL RESEARCH.

14.1. FIELD STUDIES.

1. **In order to improve understanding of the variation between different endemic areas, it is necessary to conduct studies in a range of different environments.** The studies should all follow the same protocol and use the same investigation procedures. It is also essential that the study teams have similar experience of the study methods, perhaps through a combined training programme.

2. **Before designing the study described above, it is first necessary to identify the major parameters that require quantification.** This could be done by detailed analysis of existing more extensive data sets. This procedure would allow the subsequent studies to be more focussed and they could therefore be conducted on a smaller scale.

3. **Information on the role of secondary vectors and vectors of local importance in transmission is currently lacking, and requires study, particularly in the rural areas.**

14.2. CLINICAL STUDIES.

1. **Longitudinal clinical studies on endemic populations,** with simultaneous assessment of parasitological and immunological effects, need to be carried out in order to estimate the rate of conversion from one stage to another in the natural history of the disease, and to determine long term changes in the population dynamics of disease.

2. **The effect of filariasis on mortality and life expectancy** needs to be studied from the point of view of determining its role as a precipitating factor in mortality.

3. **Estimates of the numbers of adult parasites should be obtained** in endemic areas (mF carriers as well as individuals with clinical disease) by histology of inguinal, pelvic and iliac lymphatic nodes.

15. RECOMMENDATIONS FOR RESEARCH IN IMMUNOLOGY

Diagnostic:

1. Clinical/field evaluation of the best available diagnostic antibody and circulating antigen assays following the WHO multi-laboratory comparison study in early 1991.

2. Development of antigen detection assays to detect prevalence and intensity of adult or microfilarial parasites. (Techniques and strategies for such development have already been worked out and promising leads are available).

3. Development of animal models (*B. malayi* in jirds) that can serve as a source of parasite material for production of antigens useful for diagnosis, or DNA useful for developing expression libraries.

4. Development of laboratory capability to define the immunological aspects or correlates of acute filarial fever episodes.

Serum Bank:

5. Develop a 'standard protocol' for immunological assessment of patients seen in clinic, and a routine procedure for blood collection and serum storage. This approach would allow for the assessing of many specific 'clinical-immunological' questions (see below).

Pathogenesis:

6. Develop an immunology laboratory capable of investigating antibody and cellular responses of patients to filarial infections. This laboratory would allow mechanistic and regulatory studies of the immunological component of lymphatic damage in patients with elephantiasis, hydrocele and chyluria or pulmonary damage in patients with TPE, and of renal pathology in microfilaraemic individuals pre and post treatment.

7. Develop molecular biology competence to carry out HLA type genetic studies that will allow identification of markers in individuals that determine susceptibility to infection or pre-disposition to one clinical manifestation or another.

8. Initiate long term analytical studies of maternal influences on subsequent outcomes (clinical and immunological) of exposure to filarial infection.

Protective immunity:

9. Utilize large, well defined populations to define (identify) immune individuals using all available criteria. Attempt to distinguish the immunologic response of the putatively immune population from those who are infected, in an effort to identify responses that determine protective immunity (i.e., use of "differential screening" strategy to identify difference between populations). Determine age-related changes in immunological parameters at different levels of endemicity.

10. Use insectary facilities to raise large numbers of bancrofti, L3s for use as antigen source for "differential screening" studies to define potential protective immunogens and for making cDNA libraries capable of expressing those genes encoding proteins actively produced during L3, L4 stages (ie., potential protective immunogens).

11. Develop molecular biology competence for examing recombinant proteins of protective immune potential.

16. RECOMMENDATIONS FOR CLINICAL RESEARCH

1. There is a major need to develop standardized clinical criteria as to what constitutes the clinical manifestations of disease.

2. Simultaneous parasitological, bacteriological and immunological studies need to be carried out to investigate the precipitatory factors for acute episodic attacks in filariasis patients. The role of secondary infection in the progression of lymphoedema needs to be studied.

3. The usefulness of lymphoscintography in early diagnosis of cases at risk of developing lymphoedema (particularly in mF positive cases) needs to be evaluated in community studies at different centres. It should also be evaluated for its usefulness in detecting and enumerating the locations of adult worms in relation to microfilaraemia and clinical manifestations, and as a marker of the end point of successful treatment with macrofilaricidal drugs.

4. Management of lymphoedema:

a. Clinical and other criteria should be defined for deciding the management of lymphoedema of different grades.

b. For established cases of filarial oedema in different grades, there is a need to evaluate the lymph-nodo-venous surgery developed at Tanjore.

c. Conservative management of lymphoedema with anthelmintics and other measures currently used in India, needs to be evaluated scientifically.

17. INTEGRATED RESEARCH PROGRAMME FOR DEVELOPING A DYNAMIC MODEL FRAME WORK.

Introduction:

The Seminar has generated a proposed structure for an Integrated Research Programme (IRP), which is summarized schematically in Fig:1. The main aim of the IRP is to produce a dynamic model of lymphatic filariasis allowing a quantitative assessment of the benefits (in terms of reduced morbidity) arising from the cost of control programmes. Points A, B, etc. in this structure refer to detailed recommendations for research programmes, which require completion for full implementation of the IRP. These are summarized below under a number of broad headings.

Infection and disease dynamics:

A. The age-prevalence model:

This model is largely complete in terms of describing the large scale dynamics of the acquisition and loss of infection (Vanamail et.al., 1989). The micro-spatial dynamics of infection should be examined to assess the importance of these heterogeneities. In particular, these studies should be targeted at a variety of levels; the family, the household, the street, the district etc..

B. The mF status/disease relationship:

The basic prevalence/disease model should be refined by a detailed analysis of the relationship between disease status and mF intensity based on available data. Future immunological research programmes could also make important contribution to clarifying the mechanisms and dynamics of the disease process.

C. The age-prevalence/mF blood distribution model:

A statistical model relating microfilarial prevalence and intensity as functions of host has been developed (Das et.al., 1990). The analysis of possible spatial variation in this data set would again be a fruitful research direction.

D. Vector biting rate and the success of parasite transmission:

i. Vector biting parameters. Existing data should be used to provide estimates of average biting density, both seasonally and in terms of bites per year. Experimental work to quantify the relationship between biting rate and the age and sex of the human host should be carried out.

ii. Infection of vectors. A model is required to relate the frequency distributions of microfilarial intensity in human blood and mosquitoes. This could be based on an analysis of human and entomological survey data bases.

iii. Infection by mosquitoes. Estimates of the success of parasite transmission (measured as the probability of patent infection expressed per bite) should be estimated from existing data using methods set out in the published literature.

The importance of spatial variation on the above entomological parameters should again be assessed.

E. Parasitism in the vector:

The initial transmission model will not consider the age (parity) structure of the vector population explicitly, but will encapsulate the progression of parasite larval stages through the vector population.

Analyses are required to quantify:

i. Parasite development and mortality. This can be achieved by a life table analysis of parasite survival rate, and comparison with the results of equivalent published studies.

ii. Parasite induced vector mortality can be modelled by an analysis of existing entomological data bases.

Control and socio-economics:

F. The impact of vector control on mosquito density:

The impact of IVM on the average density of vectors can be quantified from the results of the VCRC's Pondicherry project. The analysis should aim at providing a quantitative relationship between the level of effort applied in vector management and the resultant reductions in vector density. The impact of other vector control strategies (for example, larviciding or environmental modification alone) should also be assessed in this way from other data sets.

G. Chemotherapy:

i. Impact on infection. The efficacy of Chemotherapy (DEC, Ivermectin) in reducing microfilarial levels should be assessed in terms of published dose-response curves. The effect of host age on these relationship should also be examined. The model will also offer the prospect of assessing the likely impact of novel chemotherapeutic compounds and drug delivery systems, as these become available.

ii. Therapeutic effects of chemotherapy. The ability of drug treatment to alleviate morbidity and reverse or arrest pathology should be quantitatively assessed using longitudinal clinical data sets.

H. Costs and benefits of control:

Much epidemiological research proceeds in an economic vacuum, in that it does not consider the costs (and therefore the economic feasibility) of control programmes. As part of the IRP, the Seminar therefore recommends that the socio-economic studies be initiated to quantify the costs of current and proposed filariasis control programmes (and in particular IVM and various strategies for chemotherapy), as well as the benefits (in terms of the alleviation of suffering and other socio-economic indices), achieved by given reductions in morbidity. (see also the Recommendations on Socio Economic Research).

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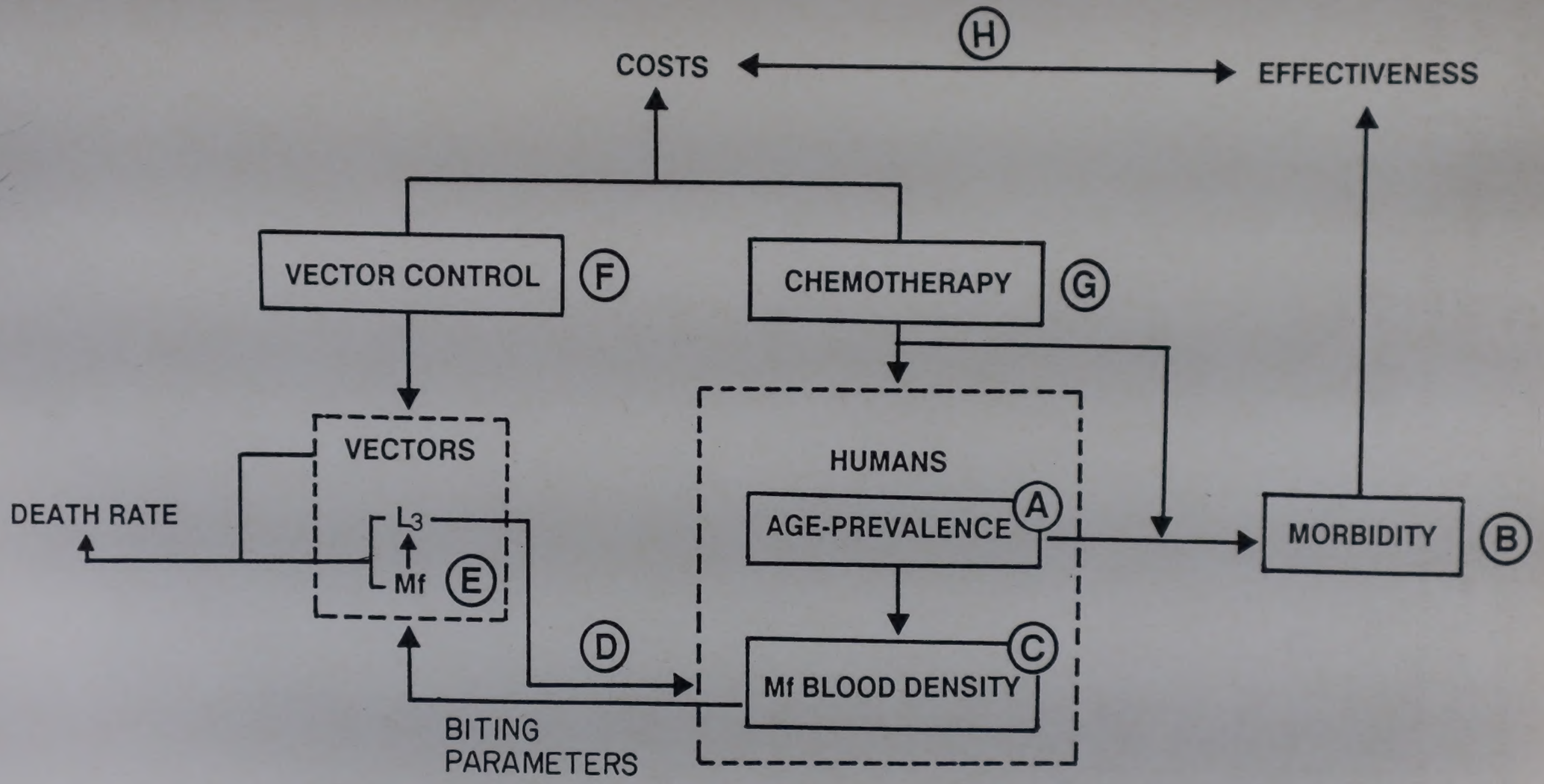
H
COSTS
EFFECTIVENESS
VECTOR CONTROL
F
CHEMOTHERAPY
G
VECTORS
HUMANS
DEATH RATE
L3
Mf
E
AGE-PREVALENCE
A
MORBIDITY
B
D
C
Mf BLOOD DENSITY
BITING
PARAMETERS

Fig. I